

REMARKS

Claims 2, 6, 16, 17, 19-21, 28 and 30 are pending in this application, claims 18 and 29 having been currently cancelled. Claims 16, 17, 19-21 and 28 have been amended and claim 30 has been added. Claims 2, 6, 16, 17, 19-21 28 and 30 are presented for reconsideration.

The opportunity to discuss this application at length with the examiner is acknowledged with appreciation.

In order to advance prosecution applicants propose to amend their claims in order to more particularly point out and distinctly claim a preferred aspect of their invention, the inventive method of preparation. Thus, composition claims 18 and 29 have been cancelled without prejudice, and claims 16, 17, 19-21 have been rewritten as method of preparation claims. New method claim 30 is supported by method claim 28. No new matter has been added.

Claims 2, 6, 10, 15-21 and 28-29, now claims 2, 6, 16, 17, 19-21 28 and 30, are finally rejected under 35 U.S.C. § 103(a) as being unpatentable over Yiv et al., U.S. Patent 6,245,349 in view of Weder WO 96/37192. Reconsideration is requested in light of the amendment *supra* and the following remarks and declaration.

Both references disclose the preparation of o/w nanodispersions by pre-mixing a phospholipid, a polyethoxylated sorbitan ester (TWEEN 80) as emulsifier, an oil, and a further component, and adding the mixture to an aqueous phase.

The examiner deems the emulsifier used in the cited references to be embraced by the term "polyethoxylated carbohydrates" of present component (b). Applicants aver that this is clearly not the case: TWEEN 80 is a polyoxyethylene sorbitan monooleate (see WO 96/37192, last line of page 11 and 1<sup>st</sup> line on page 12). Sorbitan is a cyclic ether formed by intramolecular condensation of the C<sub>1</sub> and C<sub>4</sub> of sorbitol, the alcohol derived from the carbohydrate glucose (see definition from the CTFA database and page 1059 of the textbook Wade, ORGANIC CHEMISTRY, both enclosed). Carbohydrates, polyethoxylated derivatives of which are part of present component (b), conform to the formula "C<sub>n</sub>(H<sub>2</sub>O)<sub>m</sub>", and thus may formally be regarded as being hydrates of the element carbon; an example of a carbohydrate being the monosaccharide glucose C<sub>6</sub>(H<sub>2</sub>O)<sub>6</sub>. In contrast thereto, the formula of hydrogenated sorbitol is C<sub>6</sub>H<sub>14</sub>O<sub>6</sub>, and sorbitan corresponds to a (dehydrated)

intramolecular ether thereof of the formula C<sub>6</sub>H<sub>12</sub>O<sub>5</sub>. Both sorbitan and sorbitol contain 2 hydrogens more than the corresponding carbohydrate.

The examiner asserts that Tween 80, being a derivative of a polyethoxylated carbohydrate just like sorbitol is a derivative of a sugar, falls within the genus of polyethoxylated carbohydrates of present component (b).

This conclusion (middle paragraph of page 4 of the present office action) is clearly erroneous: the complete list of emulsifiers to be used according to the present invention is defined under component (b) of present claim 28, and this definition precisely distinguishes between compound classes to be used **as such** (e.g. polyethoxylated fatty alcohols or polyethoxylated carbohydrates), and compound classes requiring or allowing a chemical modification to be used as the emulsifier (i.e. polyethoxylated vitamin E **derivatives**, polyethoxylated lanolin and the **derivatives** thereof).

There is no inclusion of any derivatives of the polyethoxylated carbohydrates of present component (b).

Thus, present component (b), *inter alia* comprising a polyethoxylated carbohydrate, clearly does not embrace a polyethoxylated sorbitan ester such as is taught in the cited primary and secondary references.

The examiner further regards Dr. Supersaxo's third declaration of May 18, 2004, as not persuasive, noting that the particle sizes obtainable using certain prior art formulations are below 50 nm and thus within the limits of the present claims, and that prior art dispersions are opalescent and transparent (see top of page 5 in present office action).

Applicants first note that the fact that particle sizes below 50 nm are obtainable using certain prior art formulations outside the claimed scope does not render the present invention obvious. Applicants have never argued that theirs is the only process capable of achieving this. Additionally, the appearance of the pharmaceutical dispersions, whether opalescent and transparent or milky (there is no talking about homogeneity in this respect), has no value of its own and just serves as a separate, visual assessment of the particle size formed.

It apparently had been agreed in the previous prosecution that present invention teaches a method of preparing a nanodispersion which is characterized by present components a-d and the sequence of mixing steps  $\alpha$  and  $\beta$ . Further delimitations which have been taken into the present claims, such as low mixing energy required, mean particle size below 50 nm, Gaussian distribution etc., are **results** of the means provided by the present invention and should not be confused with the means themselves.

There cannot be any doubt that a significant decrease of particle size, as achieved in the present invention, is an enormous advantage in the preparation of a carrier system for a lipophilic ingredient, because it is the particle size which largely determines the drug release rate. Thus, the reduction of the particle size achievable according to the present invention relative to particle sizes achievable according to the prior art is a clear advantage of the present method.

The present invention differs from the primary reference's technical teaching in the selection of specific polyethoxylated emulsifiers and the concomitant use of ethanol rather than a polyhydric alcohol. The only teaching that the secondary reference might add, if one skilled in the art would be motivated to combine these references, is the use of ethanol. In this case, one skilled in the art could only expect to achieve a result equivalent to that achieved with propylene glycol in US'349. Vice versa, the only teaching that US'349 might add to the teaching of WO'197 could make the artisan expect that replacement of TWEEN 80 by another class of emulsifiers as listed in col. 6, lines 6-36 of US'349 could result in dispersions equivalent to those of WO'197.

It has been shown in Dr. Supersaxo's second declaration, signed on December 17, 2002, however, that replacement of propylene glycol by ethanol alone already leads to a small particle size and relatively good particle homogeneity.

It has further been shown in Dr. Supersaxo's third declaration, signed on May 17, 2004, that replacement of TWEEN 80 by other polyethoxylated emulsifiers, with concomitant use of ethanol as presently claimed, leads to a reduced particle size. It deserves some emphasis in this respect that US'349 (see above-mentioned column 6) teaches equivalence of polyethoxylated as well as non-ethoxylated emulsifiers, as long as the high HLB criteria (>12) are fulfilled. However, when 2 non-ethoxylated surfactants were evaluated in the declaration, both of HLB 15, their use resulted in formation of much larger particle sizes.

Applicants submit herewith Dr. Supersaxo's fourth declaration, which presents comparisons between 2 nanodispersions containing ethanol according to the invention with nanodispersions of the same components but containing no ethanol or wherein ethanol has been replaced by propylene glycol, as employed in U.S. Patent No. 6,245,349 (Yiv et al.). Applicants aver that it could not have been expected from the combined teachings of the cited references that the present formulations would bring about a further reduction of the particle size and thus provide a distinct advantage for pharmaceutical applications.

Thus, applicants aver that the subject matter of the present invention is unobvious in the light of the prior art combination.

Reconsideration and withdrawal of the rejection of claims 2, 6, 10, 15-21 and 28-29, as applied to instant claims 2, 6, 16, 17, 19-21 28 and 30, under 35 U.S.C. § 103(a) as being unpatentable over Yiv et al., U.S. Patent 6,245,349 in view of Weder WO 96/37192, is respectfully solicited in light of the remarks *supra*.

Since there are no other grounds of objection or rejection, passage of this application to issue with claims 2, 6, 16, 17, 19-21 28 and 30 is earnestly solicited.

Applicants submit that the present application is in condition for allowance. In the event that minor amendments will further prosecution, Applicants request that the examiner contact the undersigned representative.

Respectfully submitted,



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Enclosures: Petition for Extension of Time, RCE form, Form PTO-1449, 2 references, Fee Letter, Declaration